Do the regulatory plasmablasts described here match those previously described by Shen et al. (2014)? Phenotypically, there are a number of similarities between the regulatory plasmablasts of Matsumoto et al. (2014) and Shen et al. (2014); both groups described them as $CD138^{+}CD44^{hi}CXCR4^{+}$ and possibly expressing IgM. However, a discrepancy exists in their mechanism of action. Shen et al. (2014) report a role for IL-35 production by regulatory plasmablasts whereas Matsumoto et al. (2014) could not detect IL-35 expression, either directly ex vivo or after brief PMA and ionomycin stimulation in vitro. The difference is difficult to reconcile because both groups used the same model of EAE and both isolated their cells at day 14 after EAE induction. The difference might reflect the fact that Shen et al. (2014) focus on splenic $CD138^{+}$ plasma cells, whereas Matsumoto et al. (2014) focus on $CD138^{+}CD44^{hi}$ plasmablasts in the dLN. Perhaps then the IL-35^{+} regulatory plasma cells act centrally and only IL-10^{+} regulatory plasma cells are found in inflamed lymph nodes.

In conclusion, Matsumoto et al. (2014) have provided new evidence suggesting that $Pax5^{+}$ Breg cells can differentiate into plasmablast Breg cells that upregulate IL-10 production as a result of IRF4 transcription. These findings reinforce the note of caution needed when designing new B cell and/or plasma-cell-directed therapies for the treatment of patients with autoimmune diseases or transplant recipients. Indiscriminate elimination of all plasmablast cells might lead to unexpected results due to the depletion of regulatory plasmablasts as well as autoreactive B cells and/or plasmablasts.

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IL-17 Cuts to the Chase in Colon Cancer

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Although interleukin-17A (IL-17A) facilitates colon cancer development, its target cells remain elusive. In this issue of *Immunity*, Wang et al. (2014) now demonstrate that IL-17A receptors on the intestinal epithelium promote progression of *APC* mutant adenomas associated with IL-6 expression and that IL-17A confers chemotherapy resistance.

The interleukin-17 (IL-17) family of cytokines is widely recognized for its ability to modulate inflammatory responses. Among the six IL-17 family members, IL-17A and IL-17F are best understood within lymphocyte populations. IL-17A and IL-17F share similar expression patterns and bind as ligand homo- or heterodimers to dimeric IL-17RA-IL-17RC receptor complexes to induce host defense responses against bacterial pathogens at epithelial and mucosal barriers of the skin, lung, and the colon (Gaffen, 2009). In this issue of *Immunity*, Wang et al. (2014) describe a mechanism by which epithelial IL-17RA expression enables the IL-17A-dependent progression of colon tumors via IL-6 signaling, and they identify IL-17A expression as a potential mechanism of resistance to chemotherapy.

IL-17 cytokines are produced primarily by mucosal lymphocytes, including natural killer (NK) cells, $CD4^{+}$ T helper 17 (Th17) cells, γδ Tcells, and innate lymphoid cells (ILC), and by some nonhemopoietic cells, including the Paneth cells of the small intestine. For the majority of lymphocytes, IL-17 expression is contingent on the transcription factors STAT3 and RORγt and the concerted activities of IL-6 and transforming growth factor-β (TGFβ), and the phenotype of IL-17A producing Th17 and ILC3 cells is

reinforced by IL-23 (Gaffen, 2009). Thus, many autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and allergic airway inflammation, are characterized by dysregulated IL-17A, IL-17F, and IL-23 production. Accordingly, therapeutic antibodies directed against IL-12-IL-23 (e.g., Ustekinumab), IL-17A (e.g., Secukinumab), or IL-17RA (e.g., Brodalumab) show considerable clinical benefit for patients affected by psoriasis and rheumatoid arthritis and are now being trialed for other inflammatory conditions.

A tumor-promoting role for the IL-23-IL-17 cytokine signaling axis has been identified for both inflammation-associated and sporadic cancers of the liver, stomach, and colon (Yang et al., 2014), and both cytokines are elevated in the early stages of human disease and exacerbate tumor formation in mouse models. Wang et al. now identify mature intestinal enterocytes as the IL-17RA-expressing cell population that facilitates the progression of colonic tumors in mice, although IL-17RA is also widely expressed on myeloid cells and fibroblasts. Meanwhile, IL-17RC is more commonly found on the surface of tissue-resident immune cells and, at least in humans, has a higher binding activity for IL-17F than for IL-17A (Gaffen, 2009). However, genetic loss of either IL-17RA or IL-17RC completely abolishes the cellular response to both cytokines, which otherwise result in receptor-mediated engagement of Act1 and Traf6, and activation of the MAPK-ERK and canonical NF-κB pathways (Gaffen, 2009).

In the colon cancer model used by Wang et al., adenomas arise from spontaneous loss-of-heterozygosity of the tumor suppressor *Apc* in an engineered background of heterozygous *Apc* ablation in the colonic epithelium. In humans, biallelic mutations in *APC* within the rapidly proliferating intestinal stem cells account for the initiating event in more than 80% of sporadic colon cancers, and the monoallelic mutation underpins familial adenomatous polyposis syndrome. Consistent with a pro-tumorigenic role for IL-17A, Wang et al. report that systemic IL-17RA ablation in these mice impaired tumor cell proliferation, reduced STAT3 and NF-κB activation, and increased tumor cell apoptosis. Although Wang et al. also found attenuated inflammation in the absence of IL-17RA expression, neither blood nor lymph-vessel formation were altered, nor was transcription of intestinal stem cell markers, suggesting that IL-17A might act on mature enterocytes or other cells in the tumor microenvironment. Using reciprocal bone-marrow chimeras, Wang et al. discovered that the tumor-promoting activity of IL-17RA was not mediated by hematopoietic cells, but rather by the host radio-resistant cells. These observations were corroborated by specific ablation of IL-17RA in colonic epithelial cells via a conditional *Il17ra* allele. Wang et al. verified a direct effect of IL-17A on enterocytes by stimulating organoids derived from *Apc*-deficient intestinal crypts with recombinant IL-17A, which resulted in activation of the NF-κB and MAPK signaling cascades and only minimal engagement of STAT3. In these organoids, IL-17A stimulation did not alter the excessive nuclear β-catenin accumulation that results from the loss of APC function. This observation suggests that IL-17RA signaling in the transformed mucosa regulates tumor cell proliferation independently of the aberrantly activated WNT-β-catenin signaling cascade and is akin to findings obtained in mice with impaired responsiveness of APC mutant neoplastic epithelium to IL-6 and IL-11 (Phesse et al., 2014; Putoczki et al., 2013).

Wang et al. link their in vivo observations to the ability of IL-17A to dampen the antitumor immune response of regulatory T cells and to induce the production of IL-6 and other inflammatory cytokines and chemokines. Indeed, they confirm that IL-6 deficiency reduced colonic tumor burden in their mouse model and that IL-17RA ablation in colonic epithelial cells reduced IL-6 expression in the tumors without altering expression of IL-17A or RORγt. These findings suggest that during the formation of APC mutant adenomas, the NF-κB target IL-6, via activation of STAT3, facilitates tumor cell survival, proliferation, and angiogenesis and acts down-stream of IL-17A (Figure 1). Surprisingly, IL-17RA-deficient tumors retained elevated expression of IL-11, the STAT3 activating cytokine, which most prominently supports the growth of APC mutant adenomas (Putoczki et al., 2013) and, alongside the elevated IL-1β observed by Wang et al., potentially promotes RORγt and IL-17A expression in IL-17RA-deficient tumors. Given the additive effects of IL-6 and IL-11, it remains tempting to speculate that the reduced tumor formation observed by Wang et al. in mice with enterocyte-specific IL-17RA ablation might be further impaired if one were to simultaneously also interfere with IL-11 signaling.

Thus far, IL-17A has been primarily associated with intestinal tumorigenesis in situations of chronic inflammation or commensal bacteria-associated infection (Hyun et al., 2012; Wu et al., 2009). Because bacterial stimulation of submucosal sentinels results in activation of the IL-23-IL-17 innate defense response, neutralization of these cytokines can also aggravate dextran sulfate sodium-induced colitis in mice (Ogawa et al., 2004). The observations by Wang et al. now suggest that this might be the consequence of impaired epithelial restitution mediated by IL-17RA-dependent NF-κB activation in enterocytes, and these findings are akin to similar observations involving impaired gp130-receptor-dependent STAT3 activation. Accordingly, even in the context of sporadic colon cancer, neoplastic cells might have evolved to thrive on IL-17-IL-23 wound-healing mechanisms, given that *APC* mutations decrease mucosal barrier integrity and thus lead to the release of IL-23 and IL-17 by submucosal immune cells and the subsequent growth promotion of the transformed epithelium (Grivennikov et al., 2012).

Using a model of synchronized *Apc* loss, Wang et al. observed a concomitant increase in tumor-derived IL-17A, IL-17C, and IL-17F and found that tumor initiation was reduced in mice that lacked epithelial IL-17RA expression or that had been treated with a neutralizing IL-17A antibody. Long-term administration of this antibody reduced the growth of established adenomas and enabled apoptosis and tumor shrinkage in response to 5-fluorouracil, which is one component in the chemotherapy cocktail currently used for the treatment of colon cancer. Whether therapeutic IL-17A inhibition in metastatic colon cancers, which are more clinically relevant, confers similar benefits remains to be established. This is particularly relevant in light of the findings that B16 melanoma and MC38 colon cancer cell lines show increased lung metastasis in the absence of

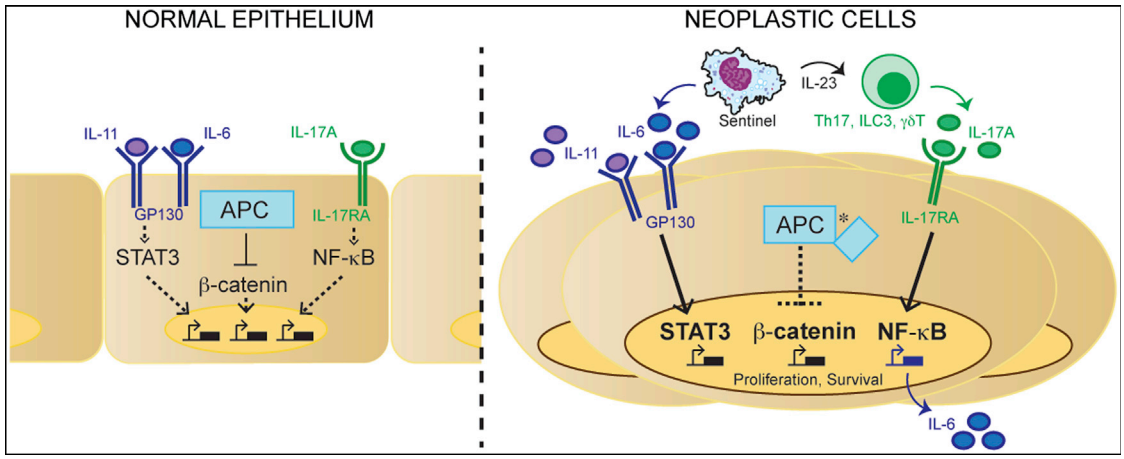

Figure 1. IL-17-Dependent Signaling Facilitates Growth of *APC* Mutant Tumors but Is Dispensable for Homeostatic Renewal of the Colonic Mucosa

Continuous renewal of the normal intestinal mucosa in the adult is governed by the Wnt-β-catenin pathway, which is negatively regulated by the *APC* tumor suppressor gene (left). In contrast, in cancer cells with excessive Wnt-β-catenin pathway activation downstream of homozygous *APC*-impairment mutations (right), Wang et al. now show that the growth of corresponding tumors requires IL-17A-dependent activation of the IL-17RA receptor on the neoplastic epithelium. At least part of this effect is attributed to NF-κB-associated IL-6 induction, which also facilitates the growth of *APC* mutant cells via the gp130 receptor-Stat3 pathway. Engagement of the later by the related IL-11 cytokine also promotes the growth of *APC* tumors, albeit independently of IL-17 signaling. IL-17 is produced by various submucosal immune cells, which require phenotype stabilization through IL-23 released from activated innate sentinel cells.

IL-17A, possibly as a result of an impaired CD8 anti-tumor immune response (Martin-Orozco et al., 2009).

The work by Wang et al. expands our knowledge of IL-17 signaling mechanisms in colorectal cancer and might inform future studies that focus on patient stratification for therapeutic treatments. Given that radiotherapy and chemotherapy remain the standard-of-care for colorectal cancer patients, it will be interesting to correlate the amount of therapy-induced damage to the nontransformed mucosa with IL-17 production and disease relapse and/or progression. It might be possible to mitigate the negative impact of anti-IL-17A-IL-17RA therapy on mucosal restitution by staggering neoadjuvent IL-17A-IL-17RA treatment with chemotherapy. It also remains to be seen whether IL-22 and other IL-23-induced cytokines can functionally substitute for IL-17A and result in acquired resistance to long-term anti-IL-17A-IL-17RA treatments. Functional redundancies of such cytokines have limited the impact of similar treatments in models of experimental autoimmune encephalomyelitis and collagen-induced arthritis.

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